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A Pathway of Cervical Sympathetic Outflow

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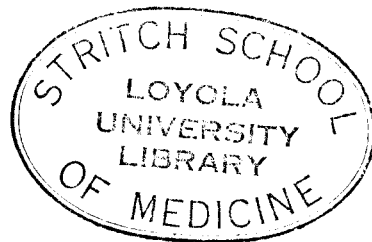
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A PATHWAY OF CERVICAL SYMPATHETIC OUTFLOW



by

John Claude McMahon

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BIOGRAPHY

John Claude McMahon was born February 2, 1941 in Chicago, Illinois. He attended Fenwick High School in Oak Park, Illinois where he graduated in June of 1959.

He subsequently attended Purdue University, Lafayette, Indiana, where he held a National Science Undergraduate Research Fellowship.

In January of 1964, he received a Bachelor of Science Degree and continued for the remainder of the school year as a graduate teaching assistant.

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ABSTRACT

Cervical ventral roots in the anesthetized dog (with skeletal muscle paralysis induced with decamethonium bromide) were cut and stimulated while records of foot pad blood flow and arterial blood pressure were made. The presence of physiologically active sympathetic outflows which supply the heart was demonstrated in some dogs. The resultant degenerating fibers of sectioned nerve roots were traced by use of the Nauta staining technique and were shown to pass by way of the vagosympathetic trunk entering the caudal cervical ganglion.

Microscopic white rami communicantes are postulated as the means by which the sympathetic fibers of segmental nerves make connections with the vagosympathetic trunk.

The presence of these pathways offers one explanation for residual sympathetic activity often observed following total extirpation of thoracic sympathetics.

INTRODUCTION

The sympathetic nervous system is a functional entity which enables the body to compensate (or adapt) to emergency situations. Although it is generally assumed to be diffuse and poorly defined, Ranson ('18) suggested it is a sequence of systematically arranged nerves much the same as is found in the central nervous system. Although the manifestations of this system are most often observed as a massive physiological response of the startled individual (e.g., vasoconstriction of the skin, dilated pupils, and increased respiratory activity (Cannon, '36), discrete reflex activity is also possible (Ury and Gellhorn, '39; Carlson et al, '41; Gellhorn et al, '46)).

The sympathetic nervous system has been the object of clinical and academic investigation for many years. Identification of its component fibers came in 1838 (Remak). In 1886, Gaskell defined the intermediolateral cell column in the spinal cord which gives rise to preganglionic fibers. Because he observed this cell column only at thoracic and lumbar levels, he proposed the name "thoraco-lumbar nervous system". He thus ruled out consideration of a cervical sympathetic outflow (Langley, '16; Sheehan, '36).

Many reseachers have since questioned his conclusions, but few have addressed themselves directly to the problem. Fewer still

have presented conclusive evidence that the sympathetic outflow is not limited to the thoracic and lumbar segments (Sheehan, '41).

Recently, work published from this department established, with physiological and histological techniques, the existence of a limited outflow of sympathetic-size fibers in the cervical region (Wiesman et al, '66). This finding contradicts the widely-accepted distribution described by Gaskell.

The purpose of this study was to determine whether some of the fibers described by Wiesman et al ('66) travel caudad within the vagosympathetic trunk transmitting impulses to the dog's heart.

REVIEW OF LITERATURE

Early histological studies by Remak (1838) identified small caliber neurons as components of the sympathetic nervous system. Bidder and Volkman (1842) confirmed this by assuming fibers of 4.1μ to 5.4μ to be sympathetic. Reissner (1862) observed that unusually large numbers of these small fibers (2μ to 4μ in diameter) are found in thoracic ventral roots as compared to cervical ventral roots. (He was misled when he found similar size fibers in dorsal roots). Schwalbe (1882) also missed their significance by postulating a relationship of fiber diameter and length.

Physiological experimentation was needed to add meaning to the anatomical findings. Continuing the classical work on vasomotion by Claude Bernard (1862), Dastre and Morat (1884) traced the small fibers responsible for this control to the intermediolateral cell column within the spinal cord. Gaskell dramatized this fact in his extensive work in 1886 in which he proposed the name "thoraco-lumbar nervous system" to characterize the levels of central origin of the sympathetic nervous system. Subsequently, Langley (1892), (1894) substantiated Gaskell's concept while directing his efforts toward further elucidation of the autonomic nervous system (Fletcher, '26).

Because no discrete intermediolateral cell column had been found at cervical levels, few researchers pursued experiments testing the origin of sympathetic fibers. Most subscribe to the concept as defined by Gaskell. Nevertheless, although cell bodies were not seen, reports of fine medullated nerves emerging from cervical levels persisted. Harmon ('00) showed the presence of visceral efferent fibers at all levels in man, but found the character and numbers to be strikingly different. Similarly, Ingbert ('04) found significant numbers of fine medullated nerve fibers in man at levels C-1 to C-3. Langley's later studies on the cat produced evidence for limited outflows of fine fibers from cervical as well as lower lumbar levels ('22).

A radical alteration in the concept of the sympathetic nervous system was suggested in 1929 when Kiss and Mihalik proposed that Gaskell's "thoraco-lumbar" outflow was too limiting. Their data, based on examination of ventral roots of a number of animals as well as man, led them to the conclusion that there is a sparse distribution of small fibers at cervical and lower levels. Although this was the logical conclusion for much of the data presented previously, most authors preferred to accept it only as the exception and therefore discounted its functional importance.

Arnell ('37) explains that his counts on ventral roots in man show that there are small caliber fibers (2μ to 3.7μ) above thoracic levels, but when compared to the tremendous numbers

found at thoracic levels their importance tends to be minimized. Similarly, Swensson ('38) found significant numbers of small fibers at cervical levels in man. His data were comparable to that for the rhesus monkey (Haggquist, '37). In a functional study on man, Bridges and Yahr ('55) have observed digital vasomotion following cervical root stimulation. They conclude that the rostral limit of sympathetic outflow must include the eighth cervical root. Sheehan ('41) conceded the possibility of cervical sympathetic outflows in man, but considered their presence rare.

The importance of basic research to ascertain the distribution of the sympathetic nervous system has best been demonstrated by clinical work. Surgical sympathectomy has been utilized to relieve Angina Pectoris and vaso-spasms of the extremity - Raynauds Disease (Raynaud, 1888; Stopford, '31; Adson, '31; Smithwick, '36). Unfortunately, after cutting all nerves which are classically regarded as sympathetic, significant numbers of individuals maintain residual sympathetic activity. Roth and Craig ('49) have presented data that several hundred individuals from more than one thousand sympathectomized patients retained residual sweating activity. This supports the findings of Ray and Console ('48).

A more striking side effect of sympathectomy has been the Horner's syndrome: a lesion of the sympathetic trunk causes

miosis, enophthalmos, and anhidrosis, whereas sectioning the third cranial nerve causes mydriasis as well as external and internal ophthalmoplegia (Horner, 1869). However, the variability of its occurrence and conflicting research data bear witness to ignorance regarding the sympathetic nerve distribution of the head and neck (Potts, '25; Kuntz, '27; Guerrier, '53). Gaskell's schema required that the head and neck derive their sympathetic innervation for the eye, glands, vessels, and arrector pili muscles from thoracic levels. Although these nerves would be expected to traverse the cervical sympathetic trunk, recently developed surgical procedures which minimize the occurrence of a Horner's Syndrome suggest the presence of a para-vertebral route as well, which escapes extirpation by classical sympathectomy (Palumbo, '66).

Attempts to explain these phenomena may be organized into several schools of thought. No single proposal removes all confusion regarding the system, however. The most logical and common conclusion is that of functional cervical outflows (Lewis and Landis, '29; Simmons and Sheehan, '39; Smithwick, '40; Mohoney et al, '41; Kirgis and Kuntz, '42; Sheehan and Pick, '43; Palumbo, '58).

A second explanation for residual sympathetic activity rests on the fact that within major nerve bundles (e.g., segmental nerves, the sympathetic trunk, and rami communicantes) one

finds regularly occurring ganglion cells now known as intermediate ganglia (Skoog, '47; Alexander et al, '49a; Alexander et al, '49b; Boyd and Monro, '49; Randall et al, '50; Wrete, '51; Ehrlich and Alexander, '51; Hoffman, '57; Boyd, '57). These ganglia allow preganglionic fibers to synapse with postganglionic cell bodies without entering any grossly visible pre- or para-vertebral ganglia. Unless the fibers do enter these centers, they escape extirpation by classical sympathectomy.

Thirdly, there are many nerves which generally are not regarded as sympathetic which are distributed so as to provide a possible route for sparse sympathetic distribution. For example, Axford ('27) has shown in man that gray rami communicantes travel with the vertebral artery to reach the stellate ganglion. A sinuvertebral nerve has been demonstrated by VanBuskirk ('41). It has its origin in sympathetic trunk ganglia and enters the vertebral canal traveling rostrad to emerge at cervical levels with segmental nerves. This nerve could also carry fibers caudad. Sheehan and Pick ('43) have proposed a more detailed classification of rami communicantes based on their study of the rhesus monkey. They point out that white rami or gray rami are seldom respectively composed entirely of pre- or postganglionic fibers and therefore one must be aware of the regular occurrence of true mixed rami above and below the thoraco-lumbar outflow. This finding would justify the proposition that preganglionic fibers may

emerge from cervical segmental nerves and be hidden in gray rami which are predominantly postganglionic fibers entering that same segmental nerve. Alexander et al ('49) have shown that functional vasomotor outflows persist after total extirpation of the sympathetic trunk. Although they did not trace the entire distribution, they have shown that the nerves do not traverse the sympathetic trunk. Other nerves grossly observable in the neck but seldom considered to be of sympathetic importance are the phrenic and vertebral nerves.

From examination of twelve dogs, Yabuki ('58) demonstrated communications between the phrenic and sympathetic trunk in ten cases on the right side and nine cases on the left. He found that the rami terminated on the ansae subclavia or caudal cervical ganglion. Histological preparations showed that 7% to 10% of the 530 to 609 fibers were myelinated. In degeneration studies, Yabuki further showed that the myelinated fibers do not degenerate when the caudal cervical and stellate ganglia are resected. This would suggest that these nerves have their preganglionic cell bodies at cervical levels.

It has been shown in the dog that the vertebral nerve carries sympathetic fibers. It has communicating rami making connections with the stellate ganglion from levels C-3 to C-7, and rami from C-7 and C-8 may also make connections with the caudal cervical ganglion. The number of myelinated fibers found in the rami at

levels C-3 to C-8 ranged from 21 to 159. These numbers were always larger than those found in the vertebral nerve, however. (Fukuyama and Yabuki, '58)

Species variation, with regard to the fundamental arrangement and numerical distribution of sympathetic fibers must always be considered (Harmon, '00; Sheehan, '41).

Because the autonomic nervous systems of the dog and man are often compared (in spite of gross differences), a review of their structures may be helpful.

The human cervical sympathetic system consists of a superior, middle, and stellate ganglion. The stellate ganglion is a dumb-bell-shaped structure formed by the fusion of the eighth cervical and first thoracic chain ganglia. The head and neck classically derive innervation by fibers from T-1 to T-5 (Kuntz, '45). The preganglionic fibers which issue from thoracic levels synapse on a number of ganglion cells (Wolf, '41). (The term "preganglionic fiber" refers to a neuron which has its cell body in the intermediolateral or intermediomedial cell columns, and leaves the spinal cord through the ventral root to synapse on ganglion cells of the pre-vertebral and para-vertebral ganglia as well as the medulla of the adrenal gland. These fibers, which in most instances are thinly myelinated, range from 1μ to 4μ in diameter (Langley, '22) or 1μ to 3.5μ (Kuntz et al, '56).

The dog differs from man in that it has no middle cervical

ganglion. It is believed that the middle cervical ganglion of man may be legitimately compared to the caudal cervical ganglion of the dog (Kuntz, '45). Thus the dog has a separate stellate ganglion separated from the caudal cervical ganglion and connected only by ansae subclavia (usually two). In addition, the dog has a fusion of the vagus nerve and the sympathetic trunk (fig.1).

In the light of data presented above, although many possible routes have been shown, the vagosympathetic trunk is the most regular and principal structure which might convey cervical sympathetic outflows caudad to the heart in the dog. Foley and Dubois ('40) have shown that the sympathetic trunk is composed of from 5,000 to 13,000 fibers, half of which are myelinated. This would mean that half are preganglionic and the remainder are postganglionic fibers. Foley ('41) further asserted that all fibers of the trunk have their origin in the superior cervical ganglion (postganglionic fibers) or through thoracic ventral roots (preganglionic fibers).

The investigations of Pannier ('46) presented evidence that cardioaccelerator fibers run via the stellate, cervical sympathetic trunk, superior cervical ganglion, and back again by the same route to the heart. However, there is reason to believe that additional fibers successively join this trunk which have their cell bodies elsewhere. For instance, Kabat ('37) has shown that cardioaccelerative effects in the atropinized dog increased as he

moved the stimulating electrode down the vagosympathetic trunk to the caudal cervical ganglion. The fibers which this finding suggests would go unnoticed unless histological fiber counts were done at many levels of the sympathetic trunk in the same dog. At best, the variations in number would be eliminated by statistical treatment. It is therefore imperative that the solution of the persistent problem of sympathetic distribution utilize both physiological and histological methods.

More recently, direct physiological evidence supported by histological preparations has been presented by Wiesman et al ('65). They stimulated cervical ventral roots of dogs while recording peripheral blood flow and arterial blood pressure. Cardiac acceleration and/or augmentation and peripheral vasoconstriction were elicited from some animals. In those same animals, histological preparations of cervical ventral roots reveal large numbers of small caliber fibers (under 3μ in diameter). They therefore conclude that a functional cervical sympathetic outflow does exist in an indeterminate percentage of dogs.

The many possible routes that nerves emerging from cervical ventral roots could take to reach the heart have been reviewed above. However, with the exception of the vagosympathetic trunk, few are significantly large and regular.

It was the purpose of this experiment to determine in the dog whether cervical sympathetic outflows as proposed by Wiesman

et al ('66) reach the heart by traversing the vagosympathetic trunk..

METHODS AND MATERIALS

Thirty-seven mongrel dogs, ranging in weight from five to eleven kilograms, were anesthetized with intraperitoneally administered Sodium Pentobarbital (Abbott Nembutal) in a dose of 32.5 mg/kg. Young dogs were chosen because they had less keratinization of their foot pads. Keratin interferes with effective light transmission to and from the photoelectric plethysmograph which was developed by Rawson ('59) to record blood flow in the paw.

Mineral oil was interposed between the plethysmograph and the paw to reduce attenuation of the light beam. Interfering radiation from external sources was eliminated by wrapping the forelimb and the receptor with metal foil.

The photoelectric plethysmograph connected to a Grass Model 5A Polygraph made permanent records of blood flow in the paw.

The femoral artery was catheterized and connected to a Statham Model P23 AC Pressure Transducer which was also connected to the Grass Polygraph. This provided a corresponding record of Arterial blood pressure.

The femoral vein was also catheterized for infusion of drugs and supportive fluid. Sterile 10% Fructose in Saline was used in a few instances.

Ultimately, an endotracheal tube was inserted so that a positive pressure respirator could be used.

The Surgery: A cervical laminectomy was performed under sterile conditions and the spinal cord exposed from the levels of the fifth to the eighth cervical segments. There was no excessive bleeding due to a midline approach. Occasional small bleeders were controlled with hemostats and no cautery was used.

The Stimulations: The stimulations had a twofold purpose:

- 1) to add support to any histological findings
- 2) to act as a screening method which would indicate physiologically which dogs would be expected to have large cervical contributions to the innervation of the heart.

Two techniques were utilized:

A) The dura mater enveloping the spinal cord was left intact. Nerve rootlets, covered by dural sheath, which enter the intervertebral foramen were picked up by means of a nerve hook. The complete nerve (consisting of dorsal and ventral roots) was severed from the spinal cord and raised free from surrounding tissue. Exuding cerebrospinal fluid from the proximal end of the cut sheath was absorbed with gauze sponges. A compound bipolar electrode was introduced into the distal portion of the sectioned nerve. (The electrode was made by inserting an insulated nichrome wire into

the bore of a four inch, 22 gauge needle which, with the exception of the very tip, had been plastic coated.) This instrument made discrete stimulation possible.

Prior to stimulation, C-10 (decamethonium bromide) in a dose of 0.2 mg/kg was injected into the femoral vein. (Decamethonium is a muscle relaxant which resembles curare and prevents muscular movement when motor nerve roots are stimulated.) When decamethonium was injected, a positive pressure respirator was connected to prevent respiratory embarrassment. Stimulation was then initiated using a Simpson Square Wave Stimulator. Stimulation parameters were: six to eight volts at a frequency of ten per second and a duration of five milliseconds - repetitive. The exact voltage delivered was monitored on an oscilloscope which was built into the stimulator. Stimulation was successively applied to cervical roots of C-6, C-7, C-8 or C-5, C-6, C-7 on one side only.

The nerves of the contralateral side were left intact as a control.

B) For the alternate procedure of stimulation, a longitudinal incision was made in the dura mater by lifting the dura away from the spinal cord with fine skin forceps and cutting the dura with iris scissors. The dura was then laid back to either side and the cerebro-spinal fluid was allowed to escape. Fluid was sponged so as to maintain a relatively dry field. The spinal cord with bundles of rootlets leaving it to enter the sheaths of the

intervertebral foramina was thus exposed. The dorsal rootlets were lifted with a nerve hook and cut. Care was taken not to injure the delicate vessels that course over the spinal cord. Decamethonium was injected as described above in procedure (A). In most cases, stimulation was applied to intact ventral roots by means of a unipolar electrode shaped as a nerve hook. The ground lead for the stimulator was connected to the large retractor which separated the neck muscles. (In some cases, the ventral roots were cut to rule out the possibility of antidromic stimulation. In these cases a ligature was tied around the bundle of ventral rootlets and they were then cut close to the spinal cord so that the distal cut end would be long enough to be raised above the surrounding tissue for stimulation as described in procedure (A) above. However, the tension put on the rootlets with this technique eventually damaged and broke them. The fine bipolar electrode was made to eliminate the many difficulties inherent in the monopolar technique.)

Closure: A piece of Gelfoam was placed over the spinal cord and the subsequent layers of muscle were closed with surgical silk. The cutaneous incision was sutured with surgical silk and covered with a gauze bandage. Colloidion was applied to the edges of the bandage to secure it to the skin. Procaine hydrochloride was injected at several points around the incision to minimize

postoperative pain when the dog became conscious.

An objective estimate of blood loss was made and, in those few cases in which it was deemed necessary, fifty to one hundred ml of sterile Fructose (10%) in Saline was injected through the femoral vein catheter.

The catheters in the femoral artery and vein were then removed, vessels tied off, and incisions sutured closed.

Postoperative Care: As a prophylactic measure following surgery, daily injections (intramuscularly) of 1ml of Terramycin were administered. The dogs were kept alive for periods ranging from four to nine days. Although a foot-drop was noted in all operated animals, all were able to walk after the operation (most within twelve hours).

Three of the thirty-seven dogs were injected with sterile 1% Trypan Blue solution (10ml/kg body weight) for three consecutive days prior to terminating the experiment. It was assumed that degenerating nerve fibers would be selectively stained (McClellan and Goodpasture, '23). This was expected to provide an alternate record to substantiate other histological findings.

Histological Preparation: All dogs were killed on the designated day by an overdose of nembutal. Some were dissected immediately for removal (in one piece) of the vagosympathetic trunk and

caudal cervical ganglion connected to the stellate ganglion by ansae. Other dogs were embalmed for succeeding dissection as described above. The fixative was ten percent formalin in all cases.

Tissues from the dogs receiving Trypan Blue injections were frozen and sectioned on a cryostat for immediate examination.

All other tissues taken by dissection were fixed five to ten days and subsequently embedded in paraffin wax (56-58°).

Longitudinal and cross sections were cut from the vagosympathetic trunk. These sections were stained by Borrel's Methylene Blue (Cottle and Mitchell, '66) as well as by Guillery's Variation of the Nauta method. A limited number of ganglion sections were stained by Glee's ('54) silver method for terminal degeneration.

All preparations were examined under a compound binocular microscope with an oil immersion objective rendering a maximum magnification of 970. Representative slides were photographed and the photographs were then enlarged.

Controls: All dogs used in the experiment had a non-operated side which served as a control.

One dog was used as a staining control. A sterile operation was performed to transect the vagosympathetic trunk on the left side only, at the level of the sixth cervical vertebra

(fig.2). The dog was maintained for six days to allow for degeneration. Portions of the vagosympathetic trunk from above and below the transection as well as from the non-operated side were sectioned and stained to provide examples of nerve tissue with variable degrees of degeneration. These tissues will be referred to in the text as "stain control" (figs. 9-11).

EXPERIMENTAL RESULTS

Surgery and Stimulation: Stimulation data varied between individuals. A representative record of changes in peripheral blood flow and arterial blood pressure due to stimulation of ventral roots at C-6 and C-8 is included (figs. 3-4). However, not all dogs show increased arterial pressure and/or decreased peripheral blood flow. Some dogs responded with a marked cardiac acceleration and augmentation with a concomitant peripheral vasoconstriction. Although this was the most convincing response, other independent variations were more frequently recorded in which only one change was noted; i.e., acceleration, augmentation, or vasoconstriction. Still other dogs showed no consistent sympathetic response but were kept alive and results of examination of their nerves are included under Histology.

All dogs showed paresis in the forelimb on the operated side with no weakness on the control side.

Histology: Histological examination of the vagosympathetic trunks taken from the operated sides of thirty-seven dogs shows the presence of degenerating fibers, whereas tissues from the non-operated side show no significant degeneration. No notable differences were found between dogs which had demonstrated a sympath-

etic response and those which had not (figs. 5-6).

Sections of segmental nerves from the operated side also show massive motor nerve degeneration (fig. 7).

Examination of the caudal cervical ganglia (stained by the Glee's method) reveals no degenerating endings.

The use of Borrel's Methylene Blue technique was found to be inferior to Guillery's Nauta method. Although both techniques show the same histological picture, all plates included herein are from the silver preparations.

Histological examination of nerves from dogs injected with the Trypan blue solution showed fibers which were differentially stained blue but cellular detail was obscured.

DISCUSSION

The lack of identical response in experimental animals to similar stimulation parameters can be explained by a number of factors. One of them is the dogs' physiological state. The age, general health, and trauma of surgery all contribute to their condition. Furthermore, the reactions of dogs to injected anesthetics may vary greatly. Randall and Peiss ('65) have studied depression of peripheral autonomic responses by sodium pentobarbital. Using heart rate as an index of depression, they stimulated the distal cut end of the vagus nerve of a dog under alpha-chloralose anesthesia. They conclude that additional small amounts of sodium pentobarbital (as little as 5mg/kg) attenuate autonomic responses. These findings are similar to those reported previously for central arousal effects (Bradley, '58) and for cardiovascular reflexes (Peiss and Manning, '64; Peiss, '64). Local vasoconstriction effects of barbiturate may also limit the range of plethysmograph records of vasoconstriction due to stimulation of sympathetics. Olmsted and Page ('66) have shown that trained dogs given barbiturates in doses of 30mg/kg show a 74% increase in peripheral resistance four hours after administration of the anesthetic. Although this peripheral change may be a manifestation of body heat conservation, one cannot as yet rule out barbiturate as a causal

factor. No reports are available on the combined effects of sodium pentobarbital and decamethonium bromide. On the strength of this study the impression emerges that the latter has a potentiating action with sodium pentobarbital because, in those cases where additional injections of decamethonium were necessary, central nervous depression was significantly prolonged.

Finally, one must consider that anatomical differences in nerve distribution may also determine the degree of physiological response. Due to the diffuse nature of the sympathetic nervous system (one preganglionic fiber may branch profusely to synapse on many postganglionic cell bodies), one would expect significant physiological responses from stimulation of a few sympathetic nerves (Cannon, '36; Wolf, '41). However, this is not always the case. Correspondingly small changes may be explained on the basis of the work of Ury and Gellhorn ('39) in which they demonstrated that physiological segmental activity is also possible in this anatomically diffuse system.

A high degree of response variability was also noted by Wiesman et al ('66) using dogs anesthetized with alpha-chloralose. On the comparative strength of data from this experiment (using barbiturate) and theirs (using chloralose) it might be assumed that physiological factors (exclusive of anesthetic effects) and anatomical factors are the principal determinants of response.

Stimulation parameters were varied for each dog to determine

a responsive range. However, all fell within the optimal ranges established by previous workers. Geohegan et al ('41) used eight volts at a frequency of 30 per second for a duration of 16 milliseconds for preganglionic stimulation. A frequency range of 15 to 20 cycles per second at a strength of three to nine volts has been determined optimal for vasomotor effects (Van Dobben-Broekema and Dirken, '50). Randall et al ('53) used 60 cycles at seven to twenty-one volts. Hare and Geohegan ('39) had also shown hypothalamic stimulation frequencies of 2 to 1600 cycles per second to be most effective.

Degenerated fibers in the vagosympathetic trunk on the side in which ventral roots were transected with no such degeneration on the control side indicates that those fibers were interrupted by the transection. That is, degenerated nerve fibers had their cell bodies within the spinal cord and were separated from them by transection of ventral roots - just as would be expected as a result of cutting thoracic ventral roots.

The cell body appears to act as the trophic center of the neuron because processes severed from it degenerate. Histological preparations from this experiment exemplify the classical picture first described by Waller (1852) and now known as secondary or Wallerian degeneration. It affects the entire length of the distal nerve segment simultaneously. Degeneration is generally believed to be initiated by the stoppage of flow of axoplasm which

thus deprives the structure of vital nutriment (Vial, '58).

Progressive changes that can be seen are (fig.8): The axon becomes distended and irregularly shaped within twelve hours. Neurofibrils lose their stainability, and by the fifth day may be found breaking down into granules. Within three days, one may also see constrictions which appear to break the myelin into ellipsoidal fragments known as digestive chambers (Weddell and Glees, '41). These fragments further degenerate into spherical droplets. The myelin is removed by macrophages which accumulate debris and appear as clumps of fatty droplets along the course of degenerating fibers (Young, '49; Nauta and Ryan, '52). From the fourth to the twenty-fifth day, Schwann cell nuclei divide and their cytoplasm increases in volume (Fisher and Turana, '63). The number of nuclei may increase thirteen-fold (Abercrombie and Johnson, '46). Thus, Schwann nuclei may fill the entire tube of degenerating nerve.

Reasons for these changes undoubtedly have biochemical basis. Cell degeneration may be attributed to such sublime changes as depletion of ribosomal RNA in the axoplasm (Lubinska, '64).

Optimal degeneration times of four to nine days were determined by pilot experiments as well as from the literature. Weddell and Glees ('41) and Lubinska ('64) point out that peripheral nerves degenerate more rapidly than components of the cerebro spinal system. However, thin axons degenerate more slowly

than thicker, more heavily myelinated axons (Nauta, '57; Fisher and Turano, '63). Furthermore, unknown factors cause some fibers to resist degeneration up to four day after separation from their cell bodies (Weddell and Glees, '41). A minimum degeneration time of four days was chosen so that all transected fibers could be demonstrated histologically. Lubinska ('64) also points out that reliable staining of peripheral nerves can be achieved after four to eight days degeneration. Many investigators have used degeneration times of five to twenty-six days for reliable staining (Evans and Hamlyn, '56; Calaresu and Cottle, '65; and Giolli, '65). Cottle and Mitchell ('66) have recently reported that complete degeneration may have taken place by twenty-five days. The use of the Nauta technique was one determining factor for the maximum degeneration time of nine days. The work of Cottle and Mitchell ('66) determined the optimal time for the use of the Nauta method. Furthermore, Evans and Hamlyn ('56) have shown that the products that are stained by the Nauta method persist longer than those stained by the Glees method. This may explain in part the failure of the Glees method in this experiment to demonstrate degeneration. It was felt that nine days maximum degeneration time would be optimal with regard to the staining technique and the size of the fibers to be examined in this experiment.

The three dogs which received one percent Trypan Blue injections did not render good frozen sections. Although occasional

blue fibers could be seen, cellular detail of the adjacent fibers was not distinct. However, corresponding sections of the vitally stained trunk were embedded and sectioned for the Nauta method.

The reliability of the Nauta technique has been proven. The plates of the "stain control" tissues are included to demonstrate cellular detail in degenerating as well as normal tissue (Figs. 9, 10, and 11). Also, extensive use of the Nauta technique over the years has led to its unquestioned acceptance. Debate regarding the Nauta technique is rather on the reactants responsible for the results. For example, Giolli ('65) has abolished Nauta silver impregnation by brominating the tissue prior to staining. He therefore concludes that unsaturated fatty acids are responsible for the reaction. Eager and Barnett ('64) report they can differentially stain large or small fibers by an oxidation treatment prior to staining with the Nauta method. The standard Nauta method principally stains axons and none of their fine branchings. Also, Lund et al ('66) have shown that membrane structures are stained when the entire procedure is used, but that neurofibrils may become the principal reactants if pre-treatment stages are omitted. Regardless of staining reactants, there can be little doubt but what the method as used in this experiment would stain degenerating elements of preganglionic fiber size.

The histological evidence presented herein is supported by stimulation records as well as by the data of previous investigat-

ors. Macroscopic fiber bundles cannot regularly be seen to connect segmental nerves with the vagosympathetic trunk in the dog. On the strength of this study, however, one must conclude that small bundles or individual fibers emerge from segmental nerves and escape unnoticed to join the trunk. These correspond to the white rami at thoracic and lumbar levels. This would seem the only explanation for the presence of degenerating fibers just anterior to the caudal cervical ganglion. Kuntz et al ('56) have suggested that in man all communicating rami contain preganglionic fibers, but that a lack of aggregations of them rostral to C-8 cause them to go unnoticed. Also, the fact that no distinct column of cells is generally demonstrable within the cervical spinal cord should not weaken this hypothesis because: (1) scattered cells similar to those of the intermediolateral cell column can be found in the cervical spinal cord (Mitchell, '53); and (2) stimulations of ventral roots of a cervical spinal cord isolated by transection will elicit sympathetic responses (Randall, personal communication).

There is also no embryological factor which conflicts with a cervical sympathetic outflow hypothesis. The cells which differentiate into sympathetic ganglia (intermediate as well as named ganglia) are derived embryologically from the ventral portion of neural tube (Kuntz, '22; Jones, '41). These fibers migrate along the course of the ventral root to ultimately form the efferent

(sympathetic) neurons.

This study has not recorded any preganglionic fiber which may have been cut by surgery, but which synapsed in an intermediate ganglion located between the point of transection and the caudal cervical ganglion. This is because the succeeding postganglionic fiber which entered the caudal cervical ganglion would appear normal by histological methods in spite of the fact that its preganglionic supply had degenerated.

Fibers which do not enter the caudal cervical ganglion by way of the sympathetic trunk (such as those traveling as fine plexus demonstrated leaving the superior cervical ganglion (Billingsley and Hanson, '18)) are not included in this study.

Photomicrographs included in this paper clearly demonstrate the normal nerves of the control and the degenerating elements of the experimental side. A legend accompanies each plate.

SUMMARY AND CONCLUSIONS

Ventral root stimulations substantiated the presence of physiologically active sympathetic outflows from cervical segments which ultimately reach the heart in some dogs.

After allowing adequate degeneration time following transection of the stimulated roots, histological preparations were made of the sympathetic trunk entering the caudal cervical ganglion.

Microscopic examination of longitudinal sections stained by the Nauta method revealed degenerating nerve fibers.

It is concluded from these findings that there are sympathetic fibers which originate at cervical spinal levels and reach the caudal cervical ganglion by traversing the vagosympathetic trunk. Diffuse connections between the caudal cervical ganglion and the heart have previously been reported.

From data presented, no conclusion can be drawn with regard to other pathways these outflows might also take to reach the heart.

The presence of white rami (similar to those at thoracic levels) which are not seen by macroscopic dissections, is postulated to explain the way in which these fibers reach the sympathetic trunk from segmental nerves.

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FIGURE 1

A drawing of major nerves in the neck of the dog which might provide pathways for cervical sympathetic outflows which ultimately reach the heart.

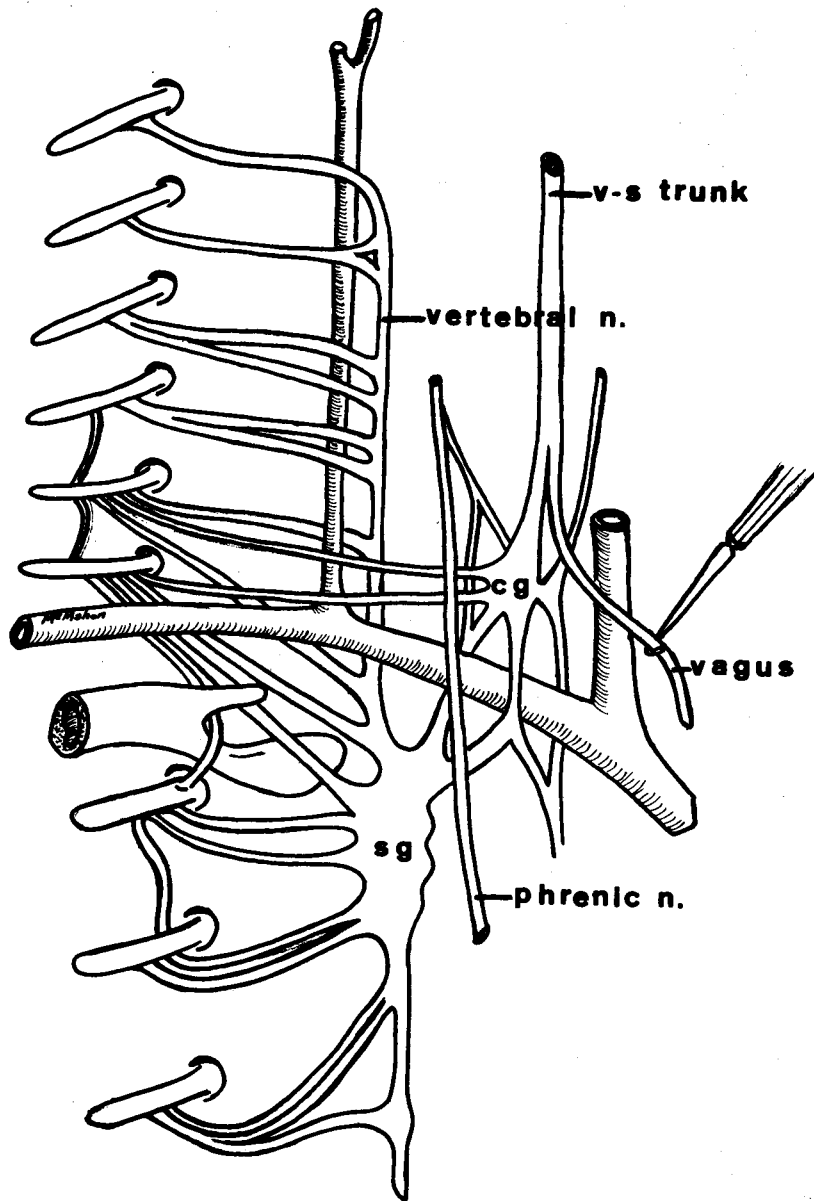


FIGURE 1

FIGURE 2

A schematized drawing of points of nerve transection and retrieval for degeneration studies. (The black bars annotated with "s" refer to points of nerve transection. Circled areas of nerve trunks refer to points of histological samplings.)

The "Control" diagram outlines the operative procedures used on the "stain control" dog. The tissue at number 2 represents the "distal stain control", and that at number 3 represents the "proximal stain control". After allowing adequate degeneration time, these tissues were examined.

The "Experimental" diagram outlines four points at which ventral roots (C-5, C-6, and C-7 or C-6, C-7, and C-8) were transected. The area designated by number 1 indicates the point at which degenerating nerves were observed entering the caudal cervical ganglion following transection of ventral roots. The vagus nerve leaves the vagosympathetic trunk above the level at which histological sections were taken.

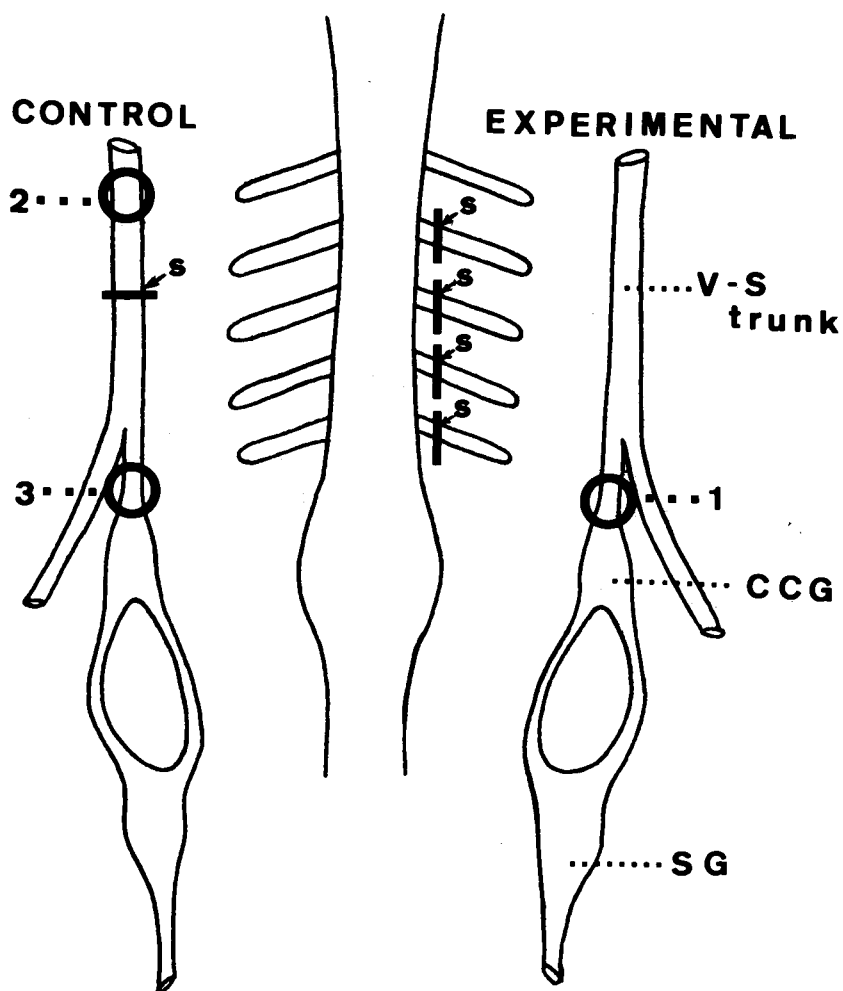


FIGURE 2

FIGURE 3

A polygraph record of an experimental dog's response to stimulation (duration indicated by dark portion of middle tracing) of an isolated distal portion of a transected ventral nerve root at C-6. Note that blood pressure rises very little (135/110 to 140/115) and the rate remains constant during the fall in blood flow in the paw.

stim. C-6

blood

flow

150-

100-

pressure

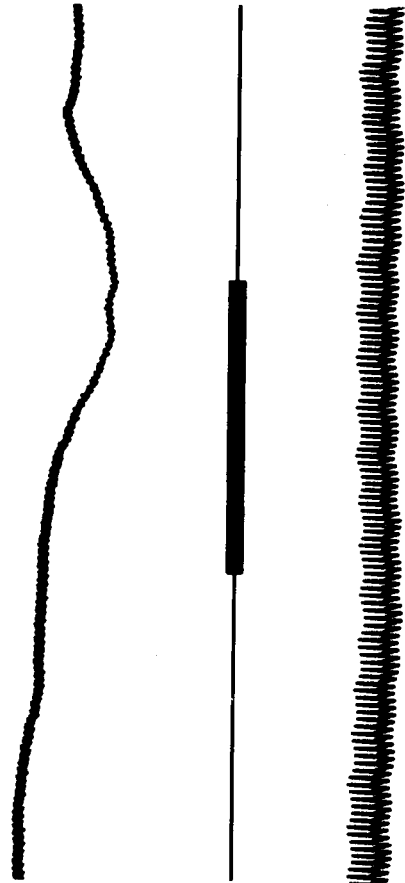


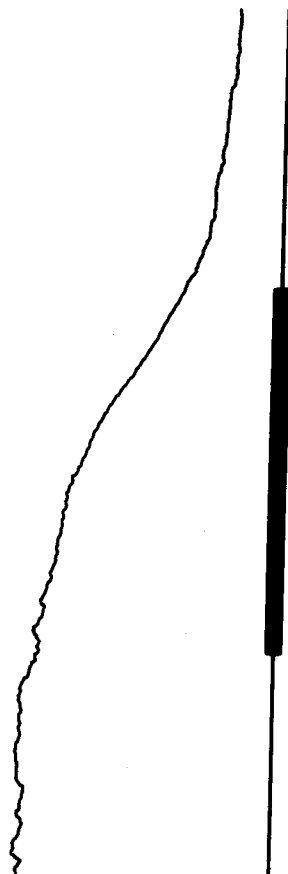
FIGURE 3

FIGURE 4

A polygraph record of the same dog described in Figure 3 during stimulation of an isolated distal portion of a transected ventral nerve root at C-8. Note that stimulation elicits an arterial blood pressure change (110/90 to 125/105) as well as a rate change from 170 to 186 beats per minute during the marked fall in blood flow in the paw.

stim. C-8

**blood
flow**



150-

100-

pressure



FIGURE 4

FIGURE 5

Sympathetic trunk fibers entering the caudal cervical ganglion on operated side of an experimental dog. Note the discrete bundles of fibers. One bundle (left) seems to be normal and intact, whereas the other (right) shows considerable degeneration (characterized by vacuolization and granulization).

Magnification of all photomicrographs - 2300X

Legend - N - neurokeratin network of normal nerve

G - granulations and elipsoidal bodies of degenerating nerve fiber

V - vacuolization of degenerating nerve fiber



FIGURE 5

FIGURE 6

Sympathetic trunk fibers entering the caudal cervical ganglion on non-operated side of dog shown in Figure 5. Note the regular arrangement of nerves. Darkly stained elements are neurokeratin network - the details of which can only be seen by careful examination with the microscope due to section thickness.

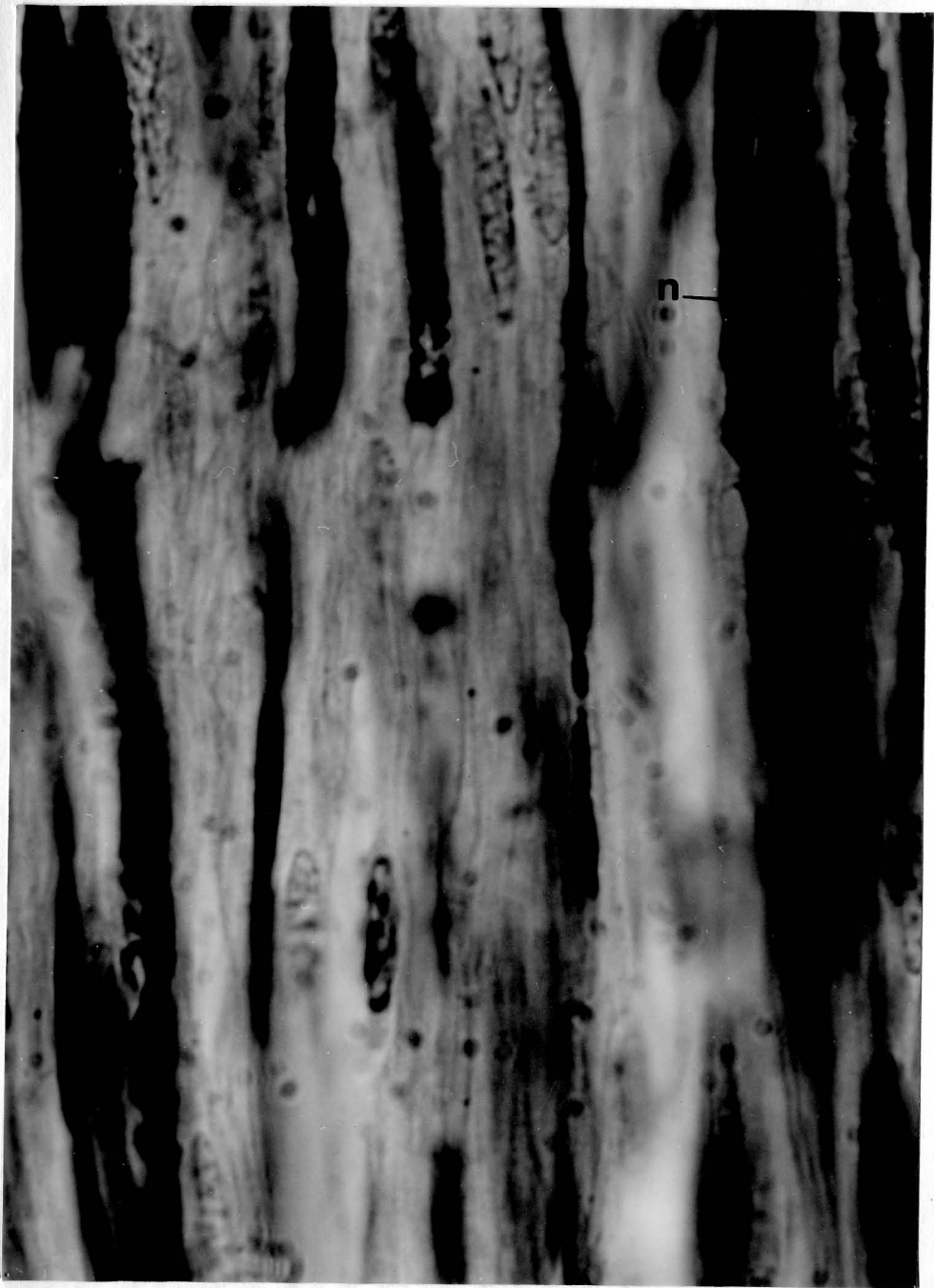


FIGURE 6

FIGURE 7

Degenerative changes which take place in the sixth cervical segmental nerve of the dog referred to in Figs 5 and 6. This degeneration verifies complete transection of the ventral nerve root indicated.

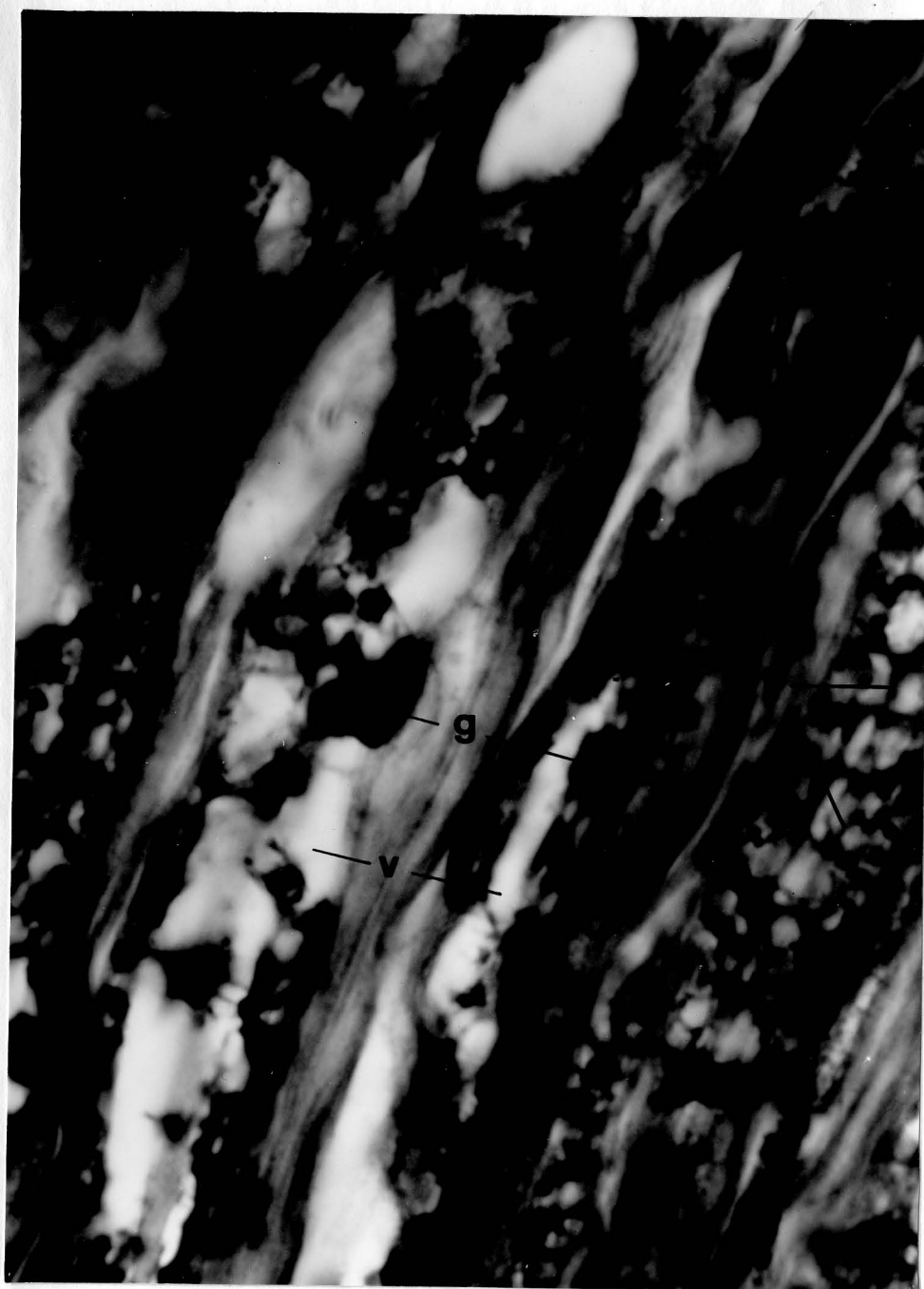


FIGURE 7

FIGURE 8

Drawing of progressive changes in nerve fiber as Wallerian degeneration takes place (after Young, '47, '49).

Legend - 1 - normal nerve representation
2 - first signs of break-down
3 - advanced degeneration

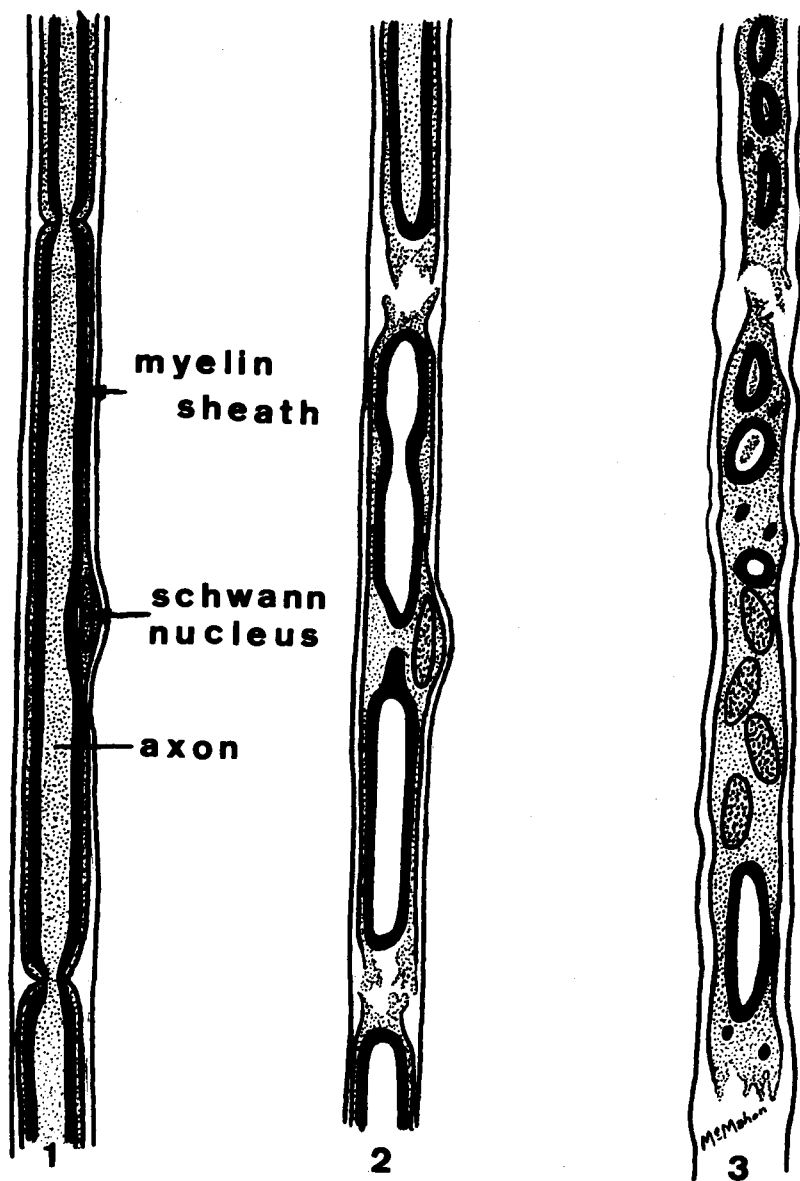


FIGURE 8

FIGURE 9

Intact sympathetic trunk from non-operated side of "stain control" dog. This tissue was taken from point corresponding to (1) on Figure 2, but no ventral roots had been sectioned. A regular, dense arrangement of fibers can be seen. (The presence of one degenerating fiber can be considered normal.)



FIGURE 9

FIGURE 10

Sympathetic trunk fibers from "stain control" dog following six days of degeneration due to transection of the vagosympathetic trunk at the level of C-5. These may also be referred to as "proximal" with respect to the caudal cervical ganglion as schematized point (3) in Figure 2.



FIGURE 10

FIGURE 11

Fibers of vagosympathetic trunk from "stain control" dog above point of transection as described in Figure 10. These may also be referred to as "distal" as schematized as point (2) in Figure 2.



FIGURE 11

APPROVAL SHEET

The dissertation submitted by John Claude McMahon has been read and approved by members of the Board of Examiners.

The final copies have been examined by the Chairman of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the dissertation is now given final approval with reference to content, form, and mechanical accuracy.

The dissertation is therefore accepted in partial fulfillment for the degree of Master of Science.

December 5 1967

Date

Leslie A. Egan

Signature of Advisor